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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/099,895	03/14/2002	Mark Andrew Guthridge	3991/0K379US0	5422

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/099,895	GUTHRIDGE ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/20/06 has been entered.

Claims 21, 22, 24 and 30-72 are canceled (claims 1-20, 23 and 25-29 were previously canceled). New claims 73-79 are added.

Claims 73-79 are under consideration in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (12/20/2005).

All objections to, and rejections of, claims 21, 22, 24, 30-37, 39-49, 52, 53 and 55-58 are moot in view of Applicants' cancellation of these claims.

Objections

The disclosure is objected to because of the following informalities:

(1) The specification contains numerous references to amino acids 582-587 of SEQ ID NO: 1 as having the sequence HRSSLP. For example, "the binding motif comprises a sequence which includes amino acids HSRSLP (SEQ ID NO: 4) corresponding to amino acids 582 to 587 of the common βc according to Figure 1 (SEQ ID NO: 1)" (pg 22, lines 26-29 of the 9/19/05 substitute specification). However, in both Figure 1 and SEQ ID NO: 1 residues 582-587 have the sequence KQASSF rather than

HSRSLP. Applicants indicate (6/20/06 response; pg 7) that this inconsistency is due to the 16 amino acid signal sequence present in SEQ ID NO: 1, and have corrected the claims to refer to residues 598-603 of SEQ ID NO: 1, which have the sequence HSRSLP. However, the specification must also be corrected throughout to refer to the correct residues in Figure 1 and in SEQ ID NO: 1.

(2) The current title of the invention, "METHOD OF REGULATING CELLULAR ACTIVITIES" is not descriptive, because it encompasses numerous cellular activities and cell types not encompassed by the claimed methods. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "METHOD OF REGULATING HEMATOPOIETIC CELL SURVIVAL".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

Claims 73-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing hematopoietic cell survival in vitro comprising mutating the sequence ^{598}HSRSLP^{603} of SEQ ID NO: 1 to ^{598}EFAAAA^{603} (or by truncating the receptor as taught by the prior art) does not reasonably provide enablement for (1) other mutations of the binding motif; (2) a method of increasing hematopoietic cell survival; or (3) a method of regulating hematopoietic cell survival in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and

8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims encompass a method of regulating hematopoietic cell survival by mutating the ^{598}HSRSLP^{603} binding motif of a receptor of SEQ ID NO: 1 (which is a GM-CSF/IL-3/IL-5 receptor). The specification teaches expression of two subunits (the α and β_c chains) of the IL-3 receptor in a CTL-EN mouse cell line. The specification reports two similar results measuring CTL-EN cell survival with wild type or mutant β_c. The specification first teaches (Example 8, pg 45) that "CTL-EN cells expressing wtβ_c remained greater than 90% viable for up to 3-4 days in the presence of either IL-3 or IL-2, cells expressing the β_cHSRSLP → EFAAAA mutant showed a loss of viability in the presence of IL-3 with only 7% viable cells remaining after 4 days (Fig. 15a)." The specification further teaches (Example 13, pg 53) "while IL-3 was able to promote viability of the CTL-EN cells expressing wtβ_c [wild type β_c chain] for up to 3 days, cells expressing the β_cHSRSLP → EFAAAA mutant showed a loss of viability in the presence of IL-3 with only 18% viable cells remaining after 3 days (Fig 24A)". The specification teaches that cell survival of the CTL-EN cells in response to IL-3 requires phosphorylation of the Ser-585 residue. [It is noted that the Serine-585 referred to in the specification is the same as serine 601 in the ^{598}HSRSLP^{603} binding motif recited in claim 73; please see the section "Objections" above for further explanation].

In view of the working example taught by the specification, the claims are enabled for a method of decreasing hematopoietic cell survival *in vitro* by mutating the ^{598}HSRSLP^{603} binding motif of a receptor of SEQ ID NO: 1 to the sequence ^{598}EFAAAA^{603}. However, the claims encompass a number of embodiments for which it is not predictable whether or not the claimed method will be functional:

(1) The claims encompass a method of regulating cell survival by mutating any residue within the binding motif ^{598}HSRSLP^{603} of SEQ ID NO: 1. The binding motif consists of six residues that can be altered either singly or in combination. Potential mutations include substitutions, deletions or additions; furthermore, other residues

outside of the binding motif may be altered in conjunction. For example, the prior art teaches that a truncated β-chain ending at residue 541 does not support growth of transfected CTLL2 cells (which are hematopoietic cells).

Considering only substitutions within the binding motif there are 20 amino acids possible at each of six positions, which represents a genus of 20^6 (6.4×10^7) different mutant binding motifs encompassed by the claims. Applicants teach that a single species of mutant motif (^{598}EFAAAA^{603}) within this genus results in decreased cell survival. It is not predictable which other mutations (either single mutations or combinations thereof) at residue 598 (histidine), 599 (serine), 600 (arginine), 601 (serine), 602 (leucine), or 603 (proline) will result in an alteration in cell survival. Changes in as little as a single amino acid residue within this region can have deleterious effects on the expressed protein. Stomski et al (1999; cited as reference 11 on the 3/14/02 Office Action) teaches that "Experiments examining the association of the β_c-585S→A point mutation with GST-14-3-3 were not possible because it is likely that this mutation introduced a cryptic proteolysis cleavage site. Flow cytometry and Western blot analysis indicated that this mutant was proteolysed and failed to be expressed on the cell surface" (pg 1937). Furthermore, the single species (^{598}EFAAAA^{603}) tested by Applicants represents a change to each of the residues within this region. The effects of mutations are often additive in combination (see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; cited previously). Therefore, it is not predictable whether not changes that alter less than all six residues will also result in decreased cell survival

(2) The claims encompass methods of increasing hematopoietic cell survival. Applicants have not identified any mutations that result in increased hematopoietic cell survival (rather than a decrease). The skilled artisan would need to test each of the genus of 20^6 (6.4×10^7) different mutant binding motifs encompassed by the claims in order to determine if any of these result in increased cell survival. It is not predictable

whether or not such experimentation would even identify a single mutation that results in an increase in cell survival.

(3) The claims encompass in vivo methods of regulating hematopoietic cell survival. Such methods include both administration of genetically altered hematopoietic cells to an animal, or transgenic animals expressing altered hematopoietic cells (in either case, the hematopoietic stem cells have a β chain with an altered ^{598}HSRSLP^{603} binding motif). Applicants' working examples are directed to in vitro hematopoietic cell survival. The relevant art teaches that cell survival of hematopoietic cells is sensitive to the environment, even *in vitro*. Guthridge et al (2000) teaches that "initial experiments performed in the presence of 10% FCS showed no defect in either the survival or growth of CTL-EN cells expressing the β_c HSRSLP→EFAAA mutant receptor (data not shown). However, a defect in survival...was observed under low serum condition" (see pg 103-104 of Guthridge et al. 2000. Molecular Cell. 6: 99-108). In view of this environmental sensitivity, it is unpredictable whether or not hematopoietic cell survival would be affected by the mutation *in vivo*. Furthermore, there are no methods or working examples disclosed in the instant application for creating transgenic multicellular animals that express the receptor, and the unpredictability in the art of creating transgenic animals in very high.

Therefore, the claims encompass numerous embodiments wherein it is unpredictable whether or not the claimed method will function. Furthermore, the combination of these unpredictable embodiments (specifically, the nature of the mutation, the ability to increase cell survival, and the ability to regulate cell survival in vivo) results in an extremely large genus of embodiments with unpredictable functionality. Due to the large quantity of experimentation necessary to determine if the claimed method could be used to regulate hematopoietic cell survival over the full scope of the claims, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan

to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

Claim Rejections - 35 USC § 112, 2nd paragraph

Claims 73-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 73 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a method step(s) wherein the survival of a hematopoietic cell is regulated. Therefore, the method steps do not achieve the goal of the preamble of "regulating hematopoietic cell survival".

Claim 73 is also indefinite because it is unclear how targeting a mutation to a binding motif relates to the goal of the preamble of the claim "regulating hematopoietic cell survival". It is unclear whether introducing the mutation in the β-chain increases or decreases cell survival.

Claim 73 is also indefinite because it is unclear what is meant by the phrase, "a cytoplasmic protein of a GM-CSF/IL-3/IL-5 receptor". The receptor is membrane-bound, so it is unclear how it can be a cytoplasmic protein.

Claim 74 is indefinite because it is unclear how the claim further limits parent claim 73. Claim 74 states "A method according to claim 73, wherein a serine or threonine residue corresponds to a serine residue at position 601." It is not clear if the "serine or threonine" residue is present in the binding motif before or after mutation of

the motif. For purposes of prosecution, the claim will be interpreted to encompass either possibility.

Claim 75 is indefinite because it is unclear how the claim further limits parent claim 73. Claim 75 states "A method according to claim 73, wherein at least two (2) amino acids at any position from 598-603 are serine." It is not clear if this limitation in claim 75 is referring to two amino acids present in the binding motif before or after mutation of the motif. For purposes of prosecution, the claim will be interpreted to encompass either possibility.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 73-79 rejected under 35 U.S.C. 102(a) as being clearly anticipated by Stomski et al (September 15, 1999; cited by Applicants as reference #11 on the 3/14/02 IDS.

It is noted that the Stomski reference includes each of the four Applicants of the instant invention as authors. However, the Stomski reference also includes six other authors who are not Applicants of the instant invention. Therefore, the Stomski reference is considered to be "by others". See MPEP 2132 III, which states, "The term "others" in 35 U.S.C. 102(a) refers to any entity which is different from the inventive entity. The entity need only differ by one person to be "by others." This holds true for all types of references eligible as prior art under 35 U.S.C. 102(a) including publications as well as public knowledge and use."

In view of the indefiniteness of the claimed method (as set forth above in the section titled "Claim Rejections – 35 U.S.C. 112, 2nd paragraph), the recitation of

"regulating hematopoietic cell survival" in the preamble of the claims from the instant application is interpreted as an intended use and bears no accorded patentable weight. Therefore, claim 73 only encompasses a method that comprises a step of "targeting a mutation to a binding motif" wherein the receptor has a β-chain of SEQ ID NO: 1 (which represents the sequence of the wild type β-chain as known in the prior art), and the binding motif has the sequence ^{598}HSRSLP^{603}.

Stomski teaches construction of a substitution mutant wherein residues ^{582}HSRSLP^{587} of the β chain are mutated to ^{582}EFAAAA^{587} (see pg 1936). Residues 582-587 of Stomski are equivalent to residues 598-603 of instant SEQ ID NO: 1 (instant SEQ ID NO: 1 includes the signal sequence in the numbering). Stomski teaches a method that is encompassed by each of claims 73-79, and therefore Stomski clearly anticipates these claims.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 73-79 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Smith et al, 1997. The EMBO Journal. Vol 16(3): 451-464 (cited by Applicants as reference #8 on the IDS submitted 10/6/2003).

As set for the above, the recitation of "regulating hematopoietic cell survival" in the preamble of the claims from the instant application is interpreted as an intended use and bears no accorded patentable weight. Therefore, claim 73 encompasses a method that comprises the step of "targeting a mutation to a binding motif" wherein the receptor has a β-chain of SEQ ID NO: 1, and the binding motif has the sequence ^{598}HSRSLP^{603}. SEQ ID NO: 1 presented in the instant application represents the sequence of the wild type β-chain as known in the prior art. The instant specification does not provide a limiting definition of the term "mutation" and therefore the term has been interpreted to encompass any deletion, addition or substitution of the specified residues.

Smith teaches a truncated β-chain ending at residue 541 (out of 897 residues; see Figure 1). The numbering system of Smith includes the leader sequence found the β-chain (see pg 452, right column). Therefore, the residues in Smith correspond to those used in SEQ ID NO: 1 of the instant application. The truncated β-chain taught by Smith includes a deletion of residues 598-603 of the wild type receptor. Therefore, this β-chain inherently meets the definition of a "mutation" of these residues. Furthermore, Smith also demonstrates that this truncated receptor does not support growth of transfected CTLL2 cells (which meet the limitation of hematopoietic cells). Therefore, Smith clearly anticipates instant claim 73.

As set forth in the section, "Claim Rejections – 35 USC § 112, 2nd paragraph", claims 74 and 75 have been interpreted to refer to the receptor β-chain either before or after mutation. As the wild type β-chain receptor has a serine at each of position 599 and 601, claims 74 and 74 are anticipated by the teachings of Smith described above.

CTLL2 cells are T cells, which are a "species" of leukocyte (white blood cell). Therefore, the teachings of Smith described above also clearly anticipate claim 76.

As truncation of the receptor β-chain removes each of the residues of the binding motif (598-603), it inherently inhibits phosphorylation of the binding motif. Therefore, the teachings of Smith described above also clearly anticipate claims 77-79.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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